Komplikationer efter allogen stamcellstransplantation med fokus på VOD/HSOS

Meet the expert

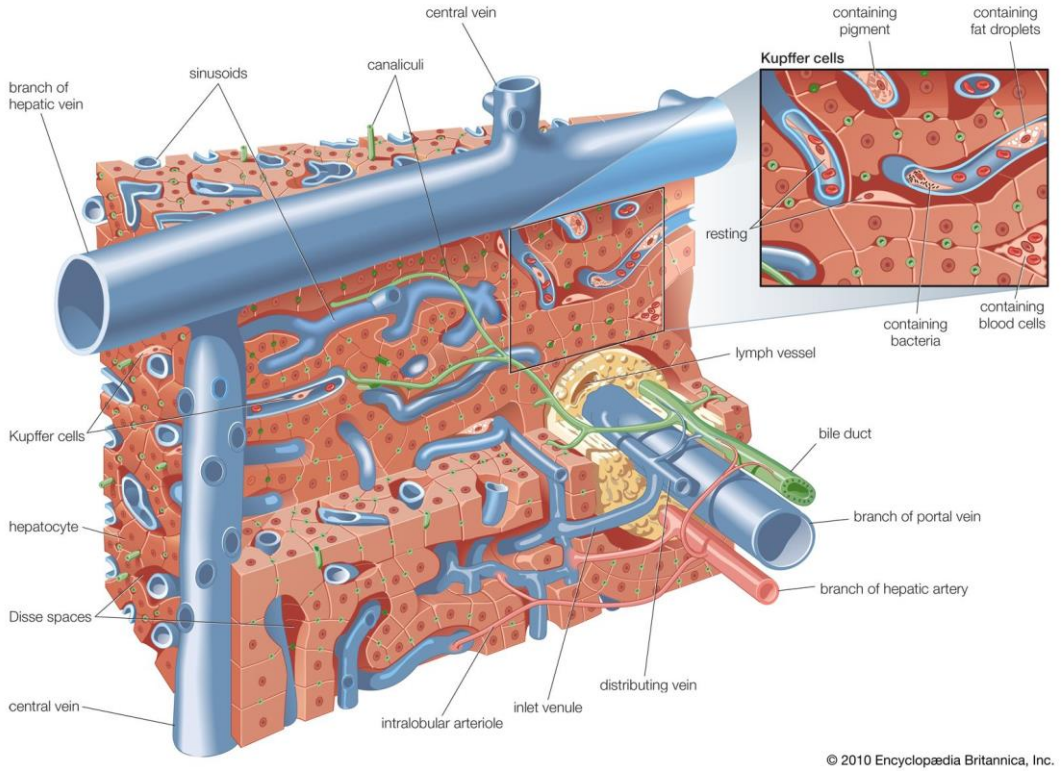
Hematologidagarna Göteborg 2023

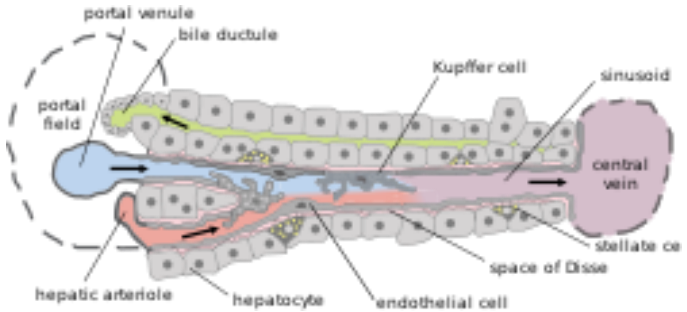
Jan-Erik Johansson

Jävsförhållanden: Inga

HSOS
Vad är sinusoider och varför sker skadan just här?

- Metabolism av vissa substanser (tex cyklofosfamid) sker via cytokrom p450-systemet vilket producerar toxiska metaboliter (tex acrolein)
- Enzymsystem (tex glutatione) omvandlar normalt dessa toxiska metaboliter till stabila, icke toxiska dito
- Vid nedsatt kapacitet i ”glutation-systemet” (medfött el inducerat/cyklo, Bu, TBI, leversjukdom) metaboliseras inte toxiska metaboliter och nivån av tex acrolein stiger
- Området kring sinusoiderna (runt centrilubulärvener/area 3) är rikt på p450 och fattigt på glutation och därför vulnerabelt för skada





Sjukdomsmekanism

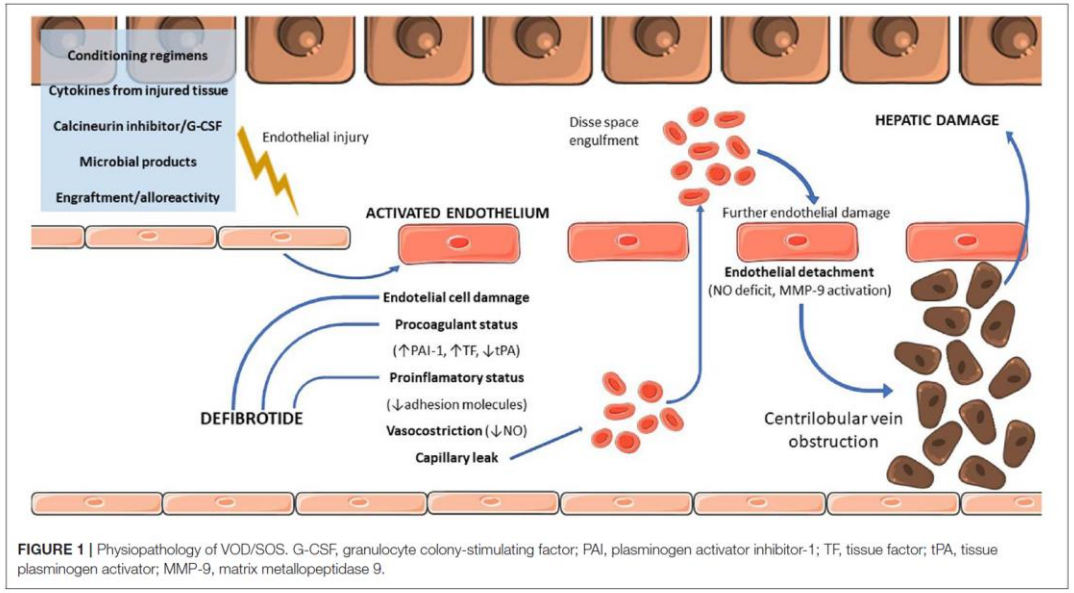


FIGURE 1 | Physiopathology of VOD/SOS. G-CSF, granulocyte colony-stimulating factor; PAI, plasminogen activator inhibitor-1; TF, tissue factor; tPA, tissue plasminogen activator; MMP-9, matrix metallopeptidase 9.

- Skada på sinusoidala epitelceller
  - Konditionering (busulfan, cyklo), MAC>RIC
  - Cytokinfrisättning - inflammation
  - Endogena mikroorganismer – translokation
  - Läkemedel (G-CSF, CNI)
  - Allo-reaktivitet T-celler (allo>auto)
- Uppluckring av epitel
- Läckage erytrocyter till Disses spatium
- Epitelet släpper
- Embolisering i levervener nedströms
  - Ökat uttryck av vWF/frisättning tissue-factor+PAI-1 leder till trombocytaggregering och pro-trombotiskt/hypo-fibrinolytiskt tillstånd (sekundärt)
- Fibrosutveckling (proliferation stellatceller/fibroblaster)
- Post-sinusoidal obstruktion
- ***Portal hypertension***

Diagnoskriterier

- ”Opinion based”/ospecifika manifestationer
- Baserade på portal hypertension – sen manifestation?
- Viktuppgång gemensam manifestation!
  - 5% viktuppgång = 3-4 kg!
  - Korrekt utgångsvikt?
- Anikterisk form (*30% barn*, 10% vuxna)
- Sen debut (40% vuxna, 15% barn)
- Incidens
  - <10% vuxna allo-MAC
  - 15-20% barn allo-MAC
  - <3-4% auto/allo-RIC

TABLE 1 | Modified seattle, Baltimore, and EBMT diagnostic criteria in adults **(A)** and in children **(B)**.

(A) ADULTS

Modified Seattle criteria[a]	Baltimore criteria[a]	EBMT criteria[a]	
Presentation within 20 d from HSCT of ≥2 of the following: – Bilirubin >2 mg/dL – Hepatomegaly, right-upper quadrant pain – Weight gain >2% over baseline due to fluid retention	Within 21 d from HSCT bilirubin ≥2 mg/dL and at least 2 of the following: – Painful hepatomegaly – Weight gain >5% – Ascites	Classical VOD/SOS[a] Within 21 d from HSCT bilirubin ≥2 mg/dL and ≥2 of the following: – Painful hepatomegaly – Weight gain >5% – Ascites	Late-onset VOD/SOS[a] Classical SOS beyond day 21, OR Histologically proven SOS OR ≥2 of the classical criteria AND ultrasound (US) or hemodynamic evidence of SOS

(B) CHILDREN

No time onset limitation for SOS/VOD occurrence

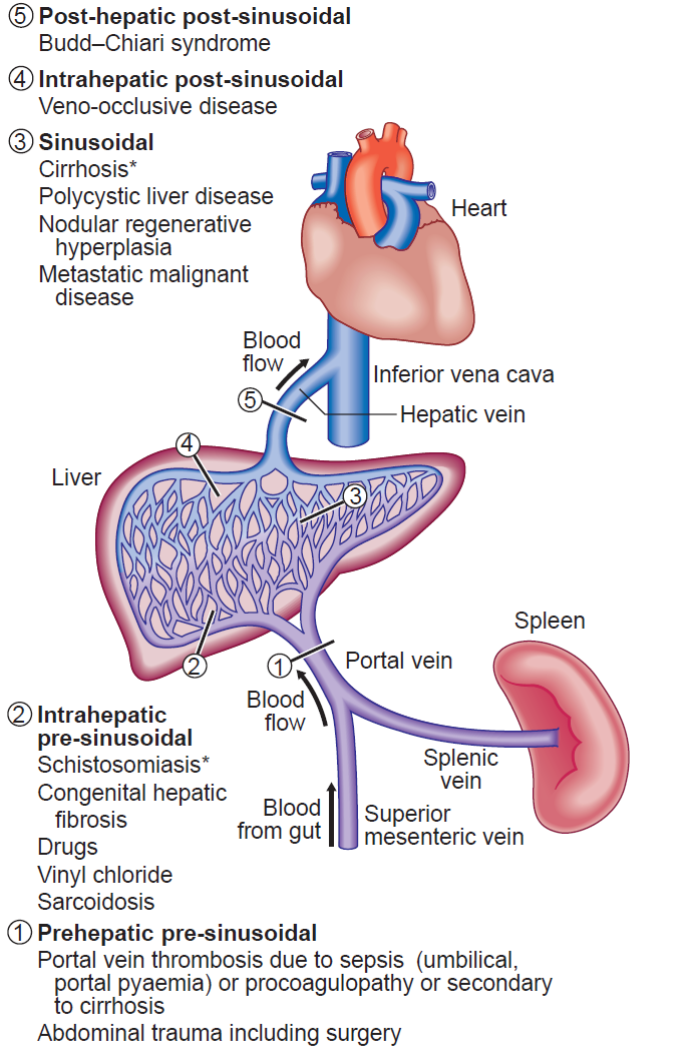
The presence of ≥2 of the following parameters[b]:

- Unexplained refractoriness to platelets transfusions defined as ≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.[c]
- Otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics or a weight gain >5% above baseline value
- Hepatomegaly (best if confirmed by imaging such as US, CT or MRI) above baseline value measured pre-HSCT
- Ascites (best if confirmed by imaging such as US, CT or MRI) above baseline value measured pre-HSCT
- Increase of bilirubin above baseline value on 3 consecutive days or bilirubin ≥2 mg/dL within 72 h

[a] *These symptoms/signs should not be attributable to other causes.*
[b] *With the exclusion of other potential differential diagnoses.*
[c] *One or more weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.*
CT, computed tomography; HSCT, hematopoietic stem cell transplantation; MRI, magnetic resonance imaging; US, ultrasonography.

Differentialdiagnoser

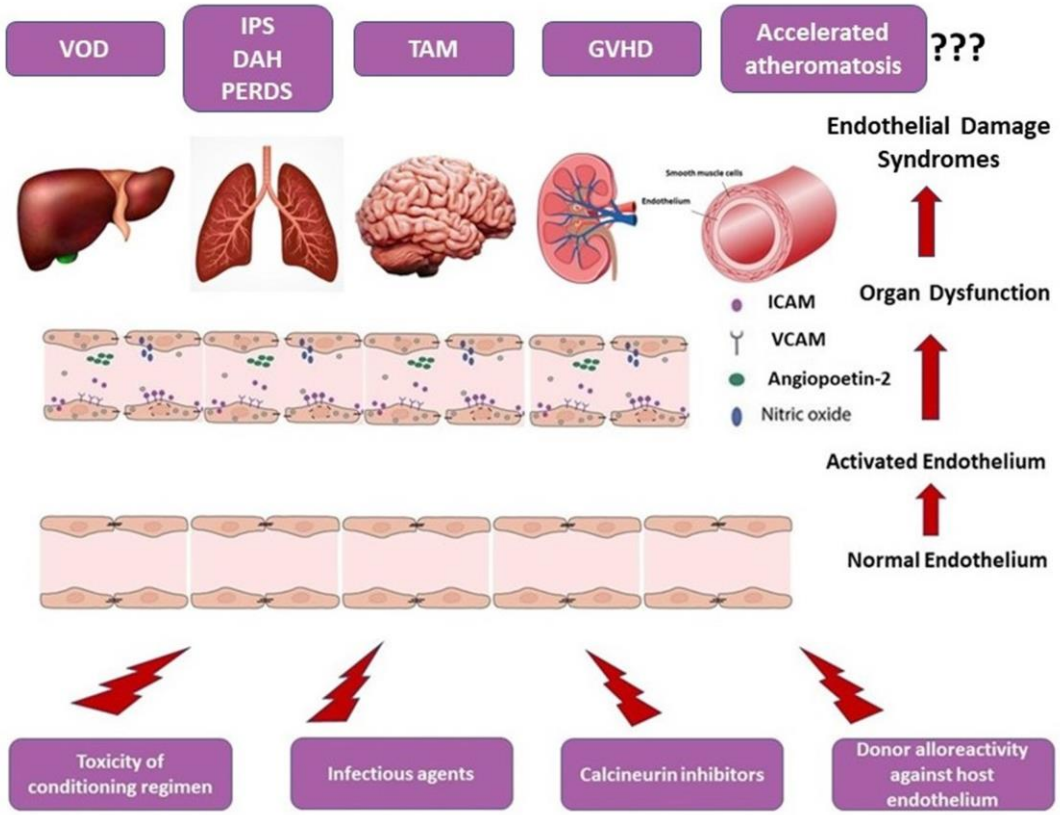
- Portal hypertension annan genes
  - Hjärtsvikt – konstriktiv perikardit
  - Cirrhos/ascites
  - Budd-Chiari
  - Portavenstrombos
- Läkemedel (DILI)
  - svampläkemedel? Vorikonazol
  - TPN?
- Sepsis
- Infektiös hepatit
- Lever GVHD



Causes of portal hypertension according to site of vascular obstruction. *Most common cause. Note that splenic vein occlusion can also follow pancreatitis, leading to gastric varices.

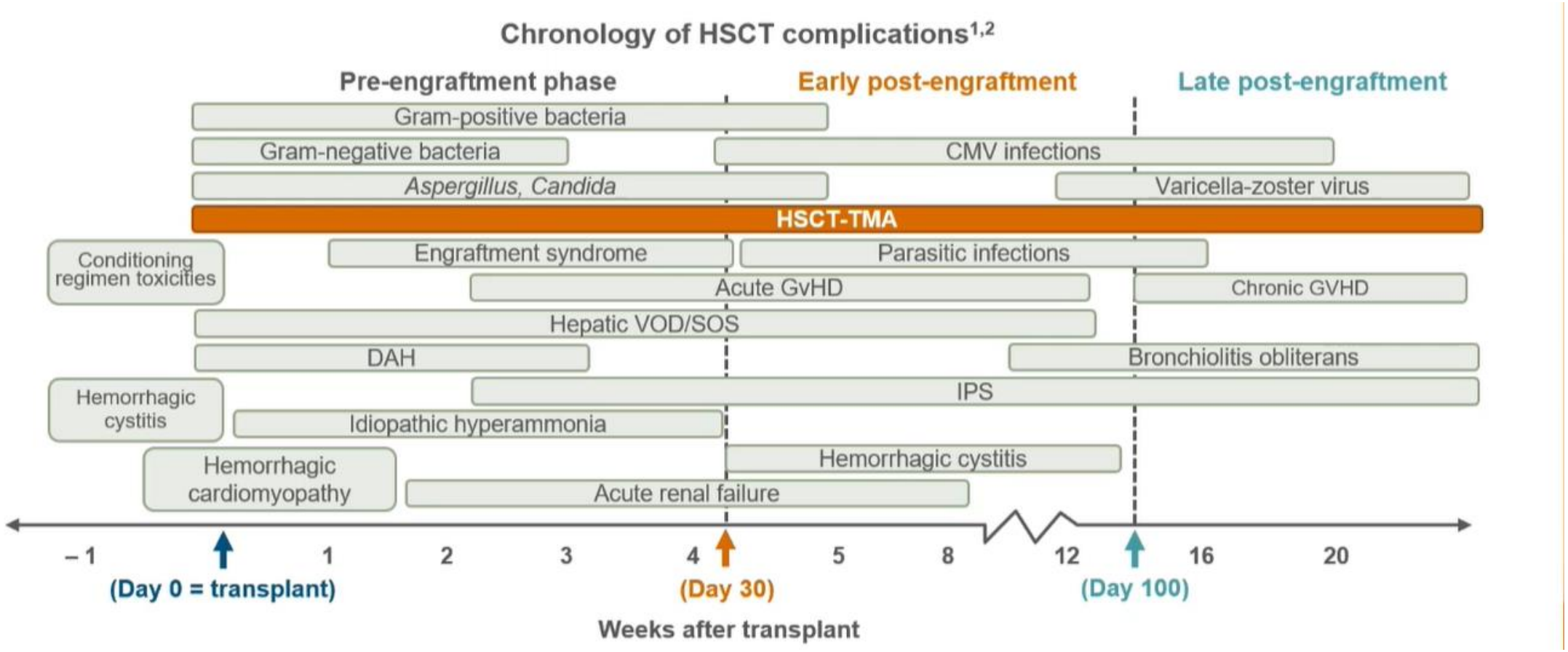
Source : Davidsons Essentials of Medicine, 2e

Endothelial dysfunction syndromes – ett vidare begrepp



- Endotelskada på kapillärnivå
- Oftast före dag 100
- Diagnos bygger på kliniska tecken och ospecifika lab – kliniska *syndrom*
- Överlappande kliniska manifestationer – svår diagnostik
- Obehandlade kan utvecklas till MOF

VOD kan förekomma samtidigt med andra endotelcellsdysfunktionssyndrom



Diagnostiska hjälpmedel

Undersökningar

- Leverbiopsi (transvenös/perkutan med gelplugg)
  - Transjugulär tryckmätning (transvenös)
  - Risk falskt negativ – fokalt eng
  - Kan utesluta differentialdiagnos (GVHD)
- Leverstelhet – Elastogram-HVPG
  - Icke invasiv
  - Undersökarberoende
  - Ej validerad metod – studier pågår
    - Tidig diagnostik?
    - Monitorering behandlingsrespons?

Blodprover

- Biomarkörer
  - *Hemostas/koagulation*
    - **PAI-1**
  - *Endotelcellsskada*
    - Von Willebrand faktor
    - Trombomodulin
    - Löslig intercellulär adhesionsmolekyl 1 (ICAM1)
    - Angiopoietin 2
    - Hyaluronsyra
  - *Inflammation*
    - IL-6
    - IL-10
    - CD97

Riskfaktorer

Table 1. Risk factors for SOS/VOD

Transplant-related factors
Unrelated donor
HLA-mismatched donor
Non T-cell-depleted transplant
Myeloablative-conditioning regimen
Oral or high-dose busulfan-based regimen
High-dose TBI-based regimen
Second HCT
Patient and disease-related factors
Older age
Karnofsky score below 90%
Metabolic syndrome
Female receiving norethisterone
Advanced disease (beyond second CR or relapse/refractory)
Thalassemia
Genetic factors (GSTM1 polymorphism, C282Y allele, *MTHFR* 677CC/1298CC haplotype)
Hepatic-related
Transaminases >2.5 ULN
Serum bilirubin >1.5 ULN
Cirrhosis
Active viral hepatitis
Abdominal or hepatic irradiation
Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin
Hepatotoxic drugs
Iron overload

Abbreviations: SOS = sinusoidal obstruction syndrome; ULN = upper limit of normal; VOD = veno-occlusive disease.

Bone Marrow Transplantation (2016) **51,** 906–912

www.nature.com/bmt

OPEN

SPECIAL REPORT

Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation

M Mohty[1,32], F Malard[1,32], M Abecassis[2,32], E Aerts[3,32], AS Alaskar[4,32], M Aljurf[5,32], M Arat[6,32], P Bader[7,32], F Baron[8,32], A Bazarbachi[9,32], D Blaise[10,32], F Ciceri[11,32], S Corbacioglu[12,32], J-H Dalle[13,32], F Dignan[14,32], T Fukuda[15,32], A Huynh[16,32], T Masszi[17,32], M Michallet[18,32], A Nagler[19,32], M NiChonghaile[20,32], S Okamoto[21,32], A Pagliuca[22,32], C Peters[23,32], FB Petersen[24,32], PG Richardson[25,32], T Ruutu[26,32], BN Savani[27,32], E Wallhult[28,32], I Yakoub-Agha[29,32], RF Duarte[30,32] and E Carreras[31,32]

Ytterligare riskfaktorer… (*Dalle et al BBMT 2015)*

Table 1
Risk Factors for Development of VOD/SOS

Risk Factors	Patient Population	Odds Ratio
Pretransplantation Risk Factors		
Age [11,12]	Ped, adults	5.2-9.5
Increased transaminase levels [4,13,14]	Ped, adults	2.4-4.6
Pre-existing liver disease [14,15]	Ped, adults	3.4
Viral hepatitis		2.0
CMV positivity		3.0
Underlying disease/advanced malignancy [11,15]	Ped, adults	
Myelodysplasia		1.5
Inborn errors of metabolism		1.8
Leukemia		2.2
CML		3.0
Immunodeficiency		3.3
Thalassemia		4.0
Interval between diagnosis of malignancy and transplantation >12 mo [11]	Ped	2.3
Deteriorated health status within 30 days before transplantation [3]		
Diarrhea	Ped	3.2
Fever	Ped	2.9
Parenteral nutrition before transplantation	Ped	3.0
Previous stem cell transplantation [14,15]		1.9
Prior abdominal radiation [14]	Adults	2.9
Prior treatment with gemtuzumab ozogamicin [16,17]	Ped, adults	19.8
Prior treatment with norethisterone [18]	Adults	10.1
Poor performance status (Karnofsky score <90%) [14,19-21]	Ped, adults	2.7
Genetic factors [22-24]		
GSTM1-null genotype	Ped, adults	4.1
Impaired pulmonary function [25]	Adults	2.4
Infection/antibiotic/antiviral use [3,26]	Ped	
Sepsis		4.1
Vancomycin during cytoreductive therapy		2.4
Pretransplantation acyclovir		4.8
Ferritin levels >1000 ng/mL [15,19,27]	Ped	3.1
Bilirubin >26 μmol/L before BMT [18,28]	Ped, adults	23.5
Transplantation-related Risk Factors		
Allogeneic versus autologous SCT [14,15]	Ped, adults	2.8
Sibling		2.8
Parental		4.6
Unrelated donor/HLA mismatch [3,14,15]	Ped, adults	1.4
Haploidentical		1.9
High-dose/myeloablative therapy [11,13,14,26,29,30]	Ped, adults	2.3-7.9
BU regimen versus others		2.6-4.5
BU + CY		3.9-5.1
Fludarabine		4.0
BCNU + CY + etoposide		2.8
High-dose total body irradiation >12 Gy + CY [3,13,14,29-31]	Ped, adults	2.8
GVHD prophylaxis [11,20,32]	Ped, adults	
Sirolimus + methotrexate + tacrolimus		~3
Methotrexate + cyclosporine		3.3
Cyclosporine		4.2
Non–T cell–depleted grafts [17,20]	Ped	2.2
Peripheral blood SCT versus BMT [33]		1.3
Acute hepatic/gut GVHD [11]	Ped	~2.0

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Gestagenpreparat:

- Primolut Nor 10 mg/dag menstruationsförskjutning dag -7 till TPK ≥ 30
- 1 studie *(Hägglund et al Blood 1998)*
  - Retrospektiv
  - MAC

Noretisteron

Norethisterone Treatment, a Major Risk-Factor for Veno-Occlusive Disease in the Liver After Allogeneic Bone Marrow Transplantation

By Hans Hägglund, Mats Remberger, Sven Klaesson, Berit Lönnqvist, Per Ljungman, and Olle Ringdén

Preparat	Aktiv substans	Dos noretisteron (mg/d)	Max konc noretisteron (ng/ml)
Primolut Nor	Noretisteron	10	18
Activelle	Noretisteron+ estradiol	0,5	3-4
Mini Pe	noretisteron	0,35	2-3
Mirena	Levonogestrel (gestagen)	1,2	0,18
Estradot Depot	estradiol	0	0

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Gemtuzumab ozogamazin *(Jametta 2016):*

	Incidens (%)
Monoterapi; dos ≤ 6mg/m2	3
Monoterapi; dos 9 mg/m2	15
Tillägg hep.tox läkemedel (tex Lanvis)	28
Allo-SCT inom 3 mån	15-40

Rekommendation

Patienter med *de novo*-AML av typ CBF-AML som ska genomgå remissionsinducerande cytostatikaterapi bör behandlas med Mylotarg 3 mg/m^2 dag 1 (till vuxen ges som regel fast dos 5 mg) i induktionskur 1 (++++). Detta förutsätter ett mycket snabbt svar på FISH alt. RTPCR-analys avseende t(8;21) och inv(16)/t(16;16) samt kännedom om LPK (ska vara <30 x 109/L). Det finns ingen evidensbas för att ge GO något eller några dagar senare än dag 1, men detta medför sannolikt inte mer toxicitet än då man ger läkemedlet dag 1.

Raritet i Europa – Verklighet i Kina: HSOS utlöst av kinesisk örtmedicin
(Wang et al BMC Gastroenterol 2018)

- Kinesisk örtmedicin innehållande pyrrolizidine alkaloider (Gynura segetum, Tusanqi)
- 132 fall/5 år ett kinesiskt centra
- 5 årsöverlevnad 60% utan defibrotide

Riskfaktorer patientfall

- Underliggande leversjukdom (PK 1,5)?
  - Perikardit & recidiv pleuriter; SLE??
- Alkoholkonsumtion? PEth?
- MAC/Busulfan högdos
  - PO el IV?
  - Behövs koncentrationsbestämning vid IV-busulfan/vuxna?
    - Logistiskt besvärligt
    - Ingen allmänt accepterad AUC-nivå
    - Ingen övertygande dokumentation för mindre toxicitet
    - Enstaka studie med bättre överlevnad med koncentrationsstyrd dosering *(Andersson et al BMT 2017)*
- Två alkylerare (Busulfan+PTCy)

Received: 21 September 2022 | Revised: 30 November 2022 | Accepted: 14 April 2023

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International Journal of Rheumatic Diseases

WILEY

ORIGINAL ARTICLE

Study of 43 SLE patients with autoimmune liver cirrhosis: emphasis on clinical features and differences from lupus without cirrhosis

Xiao-Ying Zhang[1,2] | Yu-Xin Zhang[1] | Zi-Qiao Wang[1] | Xin-Yu Zhang[3] | Xia Zhang[1] | Jia-Yang Jin[1] | Jing Li[1] | Yu-Zhou Gan[1] | Fei Yang[4] | Yan-min Liu[5] | Yan-Ying Liu[1,6] | Zhan-Guo Li[1]

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ÖVERSIKT

Alkoholmarkören fosfatidyletanol (PEth) – så bedöms testresultatet

Värdet kan indikera men inte slå fast konsumtionsnivåer

Anders Helander, sjukhuskemist, klinisk kemi och klinisk farmakologi, Karolinska universitetslaboratoriet; institutionen för laboratoriemedicin, Karolinska institutet, Stockholm
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Therese Hansson, sjukhuskemist, Medicinsk service, Laboratoriemedicin, Region Skåne; klinisk kemi och farmakologi, Skånes universitetssjukhus Lund

Riskfaktorer patientfall

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Åtgärder vid förväntad ökad risk? – Treosulfan istället för busulfan?

- In vitro evidens
  - Clearance av treosulfan oberoende av glutation S-transferas-aktivitet
- In vivo evidens
  - Barn med högriskdiagnoser
    - Osteopetros: 60% → 0%
    - HLH: >30% → 10%

European Journal of Drug Metabolism and Pharmacokinetics (2019) 44:653–657
https://doi.org/10.1007/s13318-019-00555-x

ORIGINAL RESEARCH ARTICLE

In Vitro Study of the Enzymatic and Nonenzymatic Conjugation of Treosulfan with Glutathione

Michał Romański[1] · Franciszek K. Główka[1]

Published online: 16 April 2019

Behandling; ”Supportive care”

- Vätskebalans
  - Monitorera vikt, salt/vätskeintag, urinmätning
  - Minska extracellulärvolym med ***minsta möjliga påverkan på intravaskulär volym för bevarande av njurgenomblödning***
  - Bibehåll vikt inom 2-5% från baseline
- Ascitestappning
  - Smärtlindring, ökad lungvolym – förbättrad andning
  - ***Försiktighet !*** Hellre flera mindre dagliga volymer än en stor tappning
  - Albumin ca 8 g/tappad liter (vid större tappning)
- Dialys

Läkemedelsbehandling (EBMT Handbook 2019)

- Defibrotide vid allvarlig VOD (1B)
- Metylprednisolon (2C) – stryks i nästa version ?

Läkemedel profylax (EBMT Handbook 2019)

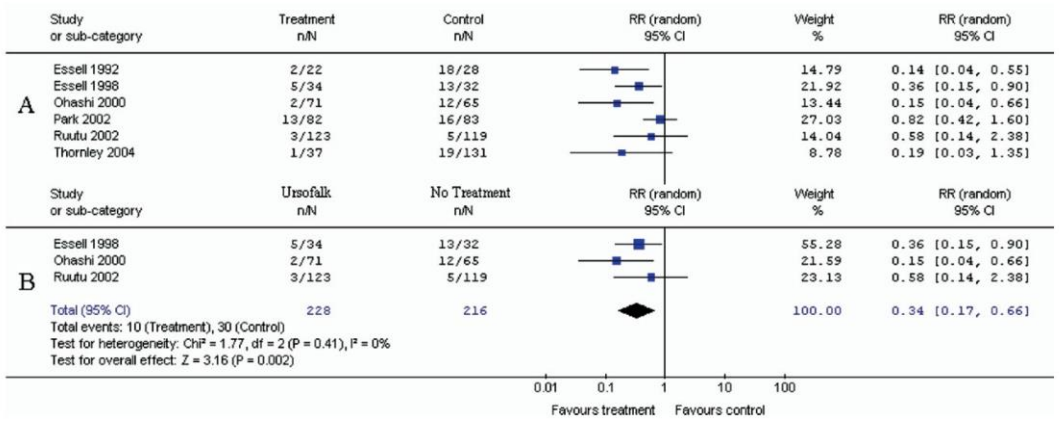
- Defibrotide; barn med hög-riskkriterier (1A)
- Defibrotide; vuxna med hög-riskkriterier (2B)
- Ursodeoxicholsyra (Ursofalk) (2C)

Defibrotide (Defitelio®)

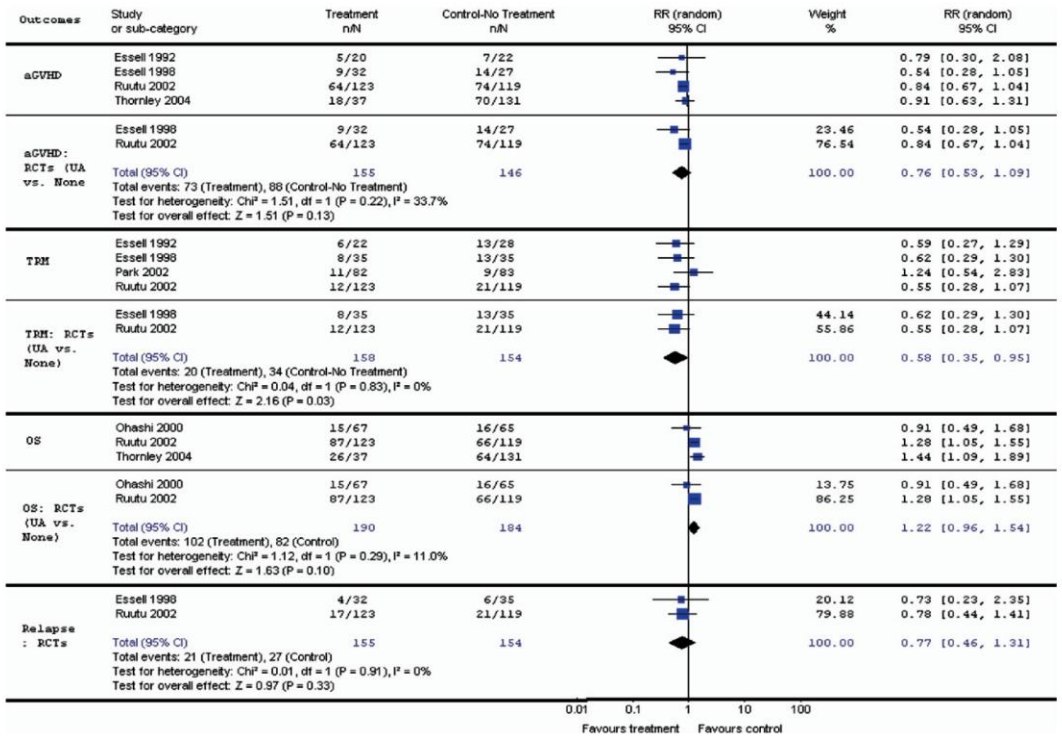
- Verkningsmekanism
  - Oligonukleotidblandning framställd från gris-tarm
  - Antitrombotisk –fibrinolytisk – antiadhesiv – antiinflammatorisk
  - Stabiliserar endotelcellsfunktion
  - Hämmad trombocytbindning/aktivering
  - Återställer trombo-fibrinolytisk balans
- Indikation (FASS)
  - *Behandling* av *allvarlig* VOD/HSOS vid HSCT hos vuxna och barn (fr 1 månads ålder)
  - Inga placebokontrollerade studier
- Biverkningar
  - Blödningar (näsblödning grad 3: 3% vs 2% i kontrollgrupp) – transfusionsgräns TPK < 30
  - Ev invasiv procedur: Utsättning ± 2 tim/kort halveringstid
- Dos – behandlingstid
  - 25 mg/kg/d (4 doser/d) – 21 dagar
- Kostnad ?
  - Ca 50 000/dygn – Knappt 1 miljon/21 dgr?

Profylax Ursofalk - metaanalys

Primär endpoint VOD



Sekundära endpoints



Defibrotidprofylax - barn

(Corbacioglu et al Lancet 2012)

- Fas 3, randomiserad
- 360 patienter – högrisk/MAC
- Primär endpoint: *VOD incidens dag +30*
- Resultat: Reduktion primär endpoint från 20% till 12% med DF (p=0,0225, ITT; p=0,0488)

	Defibrotide group	Control group	Difference in risk	p value
VOD diagnosed by day 30 (intention-to treat analysis)	22/180 (12%)	35/176 (20%)	−7·7% (−15·3 to −0·1)	..
Competing-risk analysis*	13% (8–19)	20% (15–27)	..	0·0488
Kaplan-Meier analysis	13% (9–19)	20% (15–27)	..	0·0507†
VOD diagnosed by day 30 (per-protocol analysis)‡	18/159 (11%)	34/166 (20%)	−9·2 (−17·0 to −1·3)	..
Competing-risk analysis*	11% (7–17)	20% (15–28)	..	0·0225
Kaplan-Meier analysis	11% (7–18)	21% (15–28)	..	0·0234†

Defibrotide for prophylaxis of hepatic veno-occlusive disease in paediatric haemopoietic stem-cell transplantation: an open-label, phase 3, randomised controlled trial

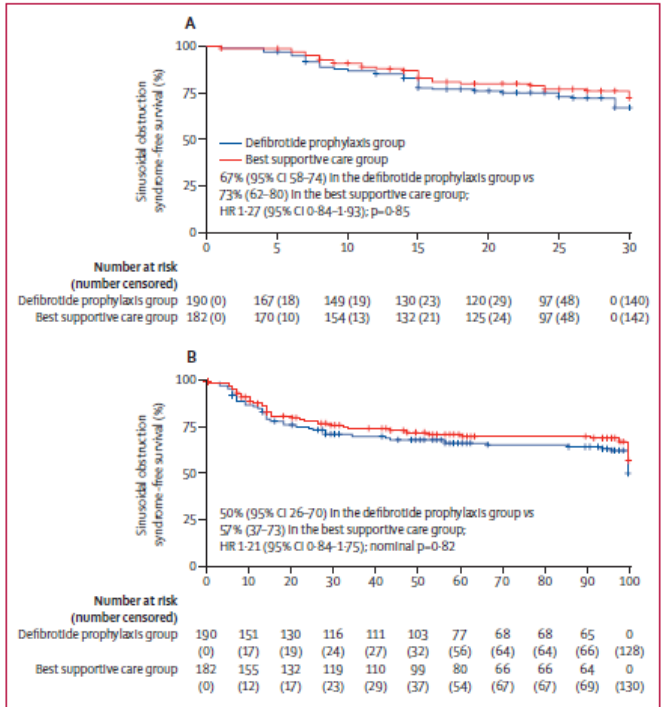
Selim Corbacioglu, Simone Cesaro, Maura Faraci, Dominique Valteau-Couanet, Bernd Gruhn, Attilio Rovelli, Jaap J Boelens, Annette Hewitt, Johanna Schrum, Ansgar S Schulz, Ingo Müller, Jerry Stein, Robert Wynn, Johann Greil, Karl-Walter Sykora, Susanne Matthes-Martin, Monika Führer, Anne O'Meara, Jacek Toporski, Petr Sedlacek, Paul G Schlegel, Karoline Ehlert, Anders Fasth, Jacek Winiarski, Johan Arvidson, Christine Mauz-Körholz, Hulya Ozsahin, Andre Schrauder, Peter Bader, Joseph Massaro, Ralph D'Agostino, Margaret Hoyle, Massimo Iacobelli, Klaus-Michael Debatin, Christina Peters, Giorgio Dini**

Defibrotidprofylax vuxna+barn (HARMONY)

- Fas-3, randomiserad
- 372 patienter (vuxna/barn)
- Högrisk/Mycket hög risk
- Primär endpoint: *VOD-fri överlevnad dag +30*
- Resultat: 67% DF vs 73% BSC (p=0.85)

Defibrotide plus best standard of care compared with best standard of care alone for the prevention of sinusoidal obstruction syndrome (HARMONY): a randomised, multicentre, phase 3 trial

Stephan A Grupp, Selim Corbacioglu, Hyoung Jin Kang, Takanori Teshima, Seong Lin Khaw, Franco Locatelli, Johan Maertens, Matthias Stelljes, Polina Stepensky, Paty Lopez, Vian Amber, Antonio Pagliuca, Paul G Richardson, Mohamad Mohty



High-risk patients*
(required to meet both criteria)

- Scheduled to receive MAC,† defined as ≥2 alkylating agents or TBI and ≥1 alkylating agent
- ≥1 of the following criteria:
  - ≥1 hepatic-related EBMT risk factor‡ at screening
  - Advanced-stage neuroblastoma requiring MAC†

Very high–risk patients*
(required to meet ≥1 criteria)

- Osteopetrosis and undergoing MAC†
  - ≥1 hepatic-related EBMT risk factor at screening
  - Advanced-stage neuroblastoma requiring MAC
- Prior treatment with an ozogamicin-containing mAb using the minimum recommended dose and schedule
  - Gemtuzumab ozogamicin (≥9 mg/m^2 total dose)
  - Inotuzumab ozogamicin (≥1.5 mg/mg^2 over 28 days)
- Class III, high-risk thalassemia

Kommentarer profylaxstudie 2023
(*Corbacioglu EBMT Paris 2023)*

- Överskattad incidens vid powerberäkning?
  - Beräknad: 28%
  - Verklig: 15% (<10% vuxna och >15-20% barn)

- ”Fel” primär endpoint (VOD-fri överlevnad dag +30)?
  - Ytterst få pat avlider i VOD före dag +30
  - Dödsfallen sker i gruppen mkt allvarlig VOD/MOF som utgör max 30-40% av VOD
  - 40% av 15% betyder att 6% av studiepopulationen kunde förväntas nå endpoint

Meta-analys defibrotide profylax

- 20 studier/3005 patienter
- Kontrollgrupp
- Både barn och vuxna
- RR profylax vs kontroller 0,30 (p=0.006)

- *Corbacioglu et al Clin Drug Invest 2022*

Key Points

This meta-analysis estimated the risk of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after intravenous defibrotide prophylaxis.

Twenty identified studies evaluated intravenous defibrotide for VOD/SOS prophylaxis.

VOD/SOS incidence was 16% in controls and 5% with intravenous defibrotide prophylaxis.

The risk ratio for developing VOD/SOS with defibrotide prophylaxis vs controls was 0.30.

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Defitelio (defibrotide): Do not use for prophylaxis of veno-occlusive disease (VOD) after post-hematopoietic stem-cell transplantation (HSCT)

Share

Gradering VOD vuxna EBMT

Corbacioglu et al BBMT 2019

Table 2
Proposed EBMT Scale for Grading VOD/SOS Severity in Adults

Clinical Measure: Highest Grade with ≥2 Symptoms	Mild	Moderate	Severe	Very Severe: All Patients with MOD/MOF
Days since first VOD/SOS symptoms*	>7	5-7	≤4	Any time
Bilirubin, mg/dL	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin, μmol/L	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics	—	—	Doubling within 48 h	—
Transaminases	≤2× normal	>2 and ≤5× normal	>5 and ≤8× normal	>8× normal
Weight above baseline	>5%	≥5% and <10%	≥5% and >10%	≥10%
Renal function	<1.2× baseline at transplantation	≥1.2 and <1.5× baseline at transplantation	≥1.5 and <2× baseline at transplantation	≥2× baseline at transplantation or other signs of MOD/MOF
Risk factor adjustment†		Mild + ≥2 risk factors	Moderate + ≥2 risk factors	
Treatment options to consider [25]	• Maintain fluid and sodium balance • Avoid hepato/nephrotoxic drugs • Careful use of diuretics • Symptomatic treatment: analgesia, oxygen, thoracentesis, paracentesis (remove <1 L/day ascites to avoid reduced renal flow) • Progression of symptoms justifies pharmacologic VOD/SOS therapy	Mild treatments plus: • If symptoms/signs persist or progress after 2 days, start pharmacologic VOD/SOS therapy • If hemodynamic data are available, start pharmacologic VOD/SOS therapy for patients with hepatic venous gradient pressure ≥10 mm Hg	Moderate treatments plus: • Start pharmacologic VOD/SOS therapy	Severe treatments plus: • Hemodialysis/ hemofiltration if required

MOF indicates multiorgan failure.

* Time from the date when the first signs/symptoms of VOD/SOS began to appear (determined retrospectively) and the date when the symptoms met VOD/SOS diagnostic criteria.

† In the presence of ≥2 risk factors, severity is considered 1 grade higher. Adapted from Richardson et al [95] with permission.

Mortalitet fortfarande hög vid allvarlig sjd

- I sjunkande
  - Allvarlig/MOF 80% → 40% i senare rapporter *(Mohty et al BMT 2023)*
  - Bättre IVA-vård
  - Bättre riskstratifiering
  - Tidigare behandling med defibrotide

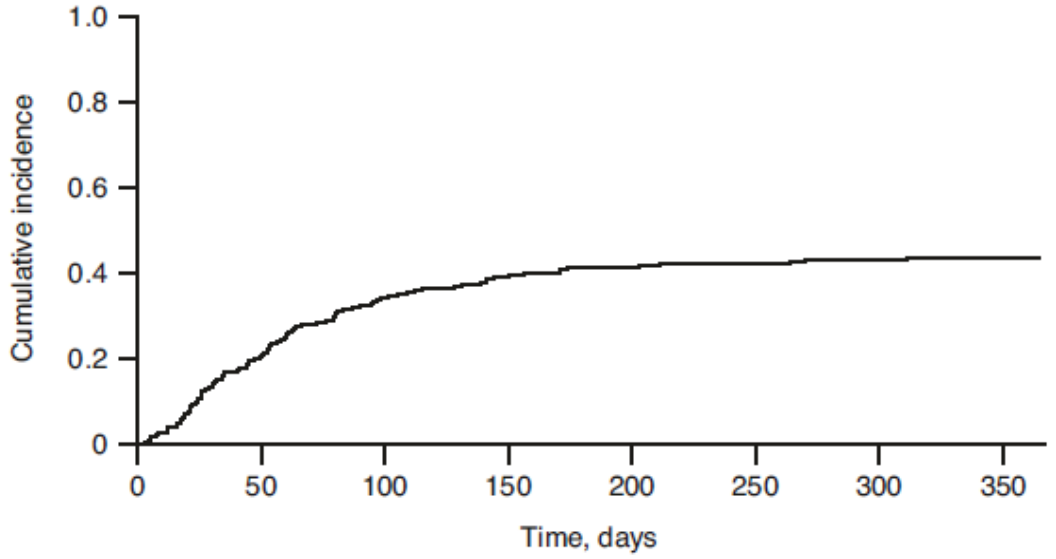
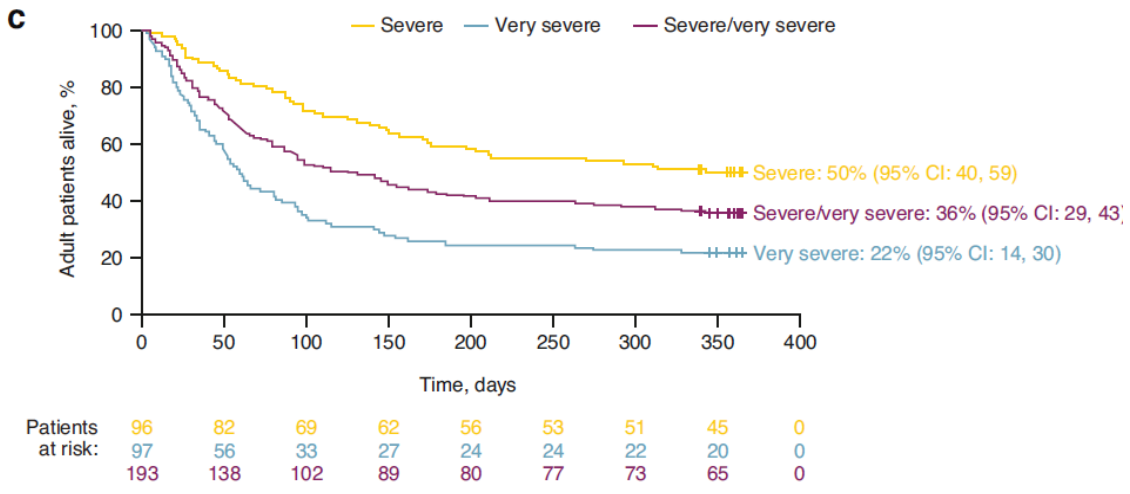


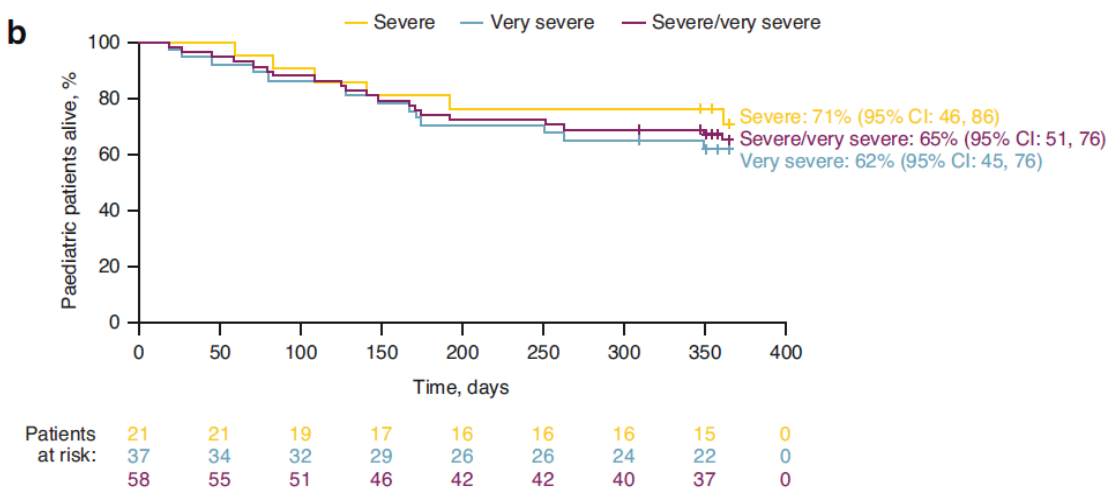
Fig. 5 Cumulative incidence of HCT-related mortality in patients with severe/very severe VOD/SOS at 12 months post-HCT. HCT indicates haematopoietic cell transplantation.

Prognos bättre för barn *(Mothy et al BMT 2023)*

Överlevnad vuxna (defibrotidbehandlade)



Överlevnad barn (defibrotidbehandlade)



Angeläget att minska risken för (svår) VOD!

- Identifiera riskindivider (på transplantationsmötet)
  - Finns riskfaktorer? T.ex.
    - PEth
    - Ferritin
- Icke farmakologiska åtgärder
  - Behandla järnöverskott – om tid finnes…
  - Tacrolimus istället för CyA?
  - Är ev levertoxiska läkemedel utsatta?
  - RIC istället för MAC? Recidivrisk?
  - Reduced toxicity conditioning; Treosulfan istället för busulfan?
- Farmakologisk profylax?
  - Ursofalk
  - Defibrotide??
- Aktiv screening – tidiga tecken (på vårdavdeln-öppenvård)
  - Viktuppgång: Korrekt utgångsvikt? 5% ≈ 3-4 kg!
  - Trombocytrefraktäritet
- Tidigt insatt behandling (”pre-emptive”)

Take home messages VOD/HSOS

Viktigaste mål: Förhindra uppkomst!

- Identifiera tidigt riskindivider – eliminera/minska risker
- Hög misstänksamhet – aktiv screening
- Släpp inte misstanken efter utskrivning från avdelning

Behandling:

- Varsam diuretikabehandling/ascitestappning; var rädd om njurgenomblödningen!
- Defibrotide: Så tidig intervention som möjligt – ”pre-emptive behandling”
    - Räds inte trombocytopeni och/eller kostnader